Review Article

Evoked potentials in the clinical neurosciences

RICHARD P. GREENBERG, M.D., PH.D., AND THOMAS B. DUCKER, M.D.

Division of Neurological Surgery, Department of Surgery, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia, and Division of Neurological Surgery, Department of Surgery, School of Medicine, University of Maryland, Baltimore, Maryland

The use of evoked potentials for the evaluation of disorders of the nervous system has become a most valuable aid to the neurosurgeon and neurologist, often providing information of critical value without recourse to invasive techniques. In order to employ these techniques, it is helpful to understand the principles of evoked potential electrogenesis and the methodology used for analysis of evoked potential clinical data. This article is aimed at providing the clinical neurosurgeon with this type of information and with a review of current clinical applications in this rapidly developing field.

KEY WORDS • evoked potentials • neurophysiology • brain tumor • head injury • spinal cord injury • spinal cord tumor • intraoperative monitoring • demyelinating disease

NEUROELECTRIC activity depends upon neuronal vitality for its realization and, like the neurological examination, is a method of assessing central nervous system (CNS) function irrespective of the presence or absence of anatomical alterations. The study of neuroelectric activity is particularly useful in uncooperative, confused, or comatose patients because it offers an evaluation of CNS function that is both complementary and supplementary to that obtained from the clinical examination. Moreover, the techniques utilized clinically to record neuroelectric potentials are noninvasive and allow frequent serial studies to be obtained at low risk to the patient.

Evoked Potentials

While the electroencephalogram (EEG) reflects “spontaneous” brain electrical activity, the sensory evoked potential represents the CNS response to the application of a specific extrinsic stimulus. Theoretically, any stimulus sufficient to cause depolarization of a peripheral, sensory, or mixed nerve can be used to evoke neuroelectric potentials in the CNS. In practice, the visual (strobe light flash, reversible checkerboard pattern), auditory (click), and somesthetic (sensory stimulus) systems

Definition of Abbreviations

ABEP = auditory brain-stem evoked potential
AEP = auditory evoked potential
EP = evoked potential
EPSP = excitatory PSP
IPSP = inhibitory PSP
MEP = multimodality evoked potential
PSP = postsynaptic potential
PVEP = reversible checkerboard pattern VEP
SBEP = somatosensory brain-stem evoked potential
SEP = somatosensory evoked potential
VEP = visual evoked potential
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FIG. 1. Multimodality evoked potential data from a normal subject. The top trace depicts an auditory brain-stem (far-field, see text) evoked potential recorded in response to left ear click stimulation. The middle trace is the somatosensory evoked potential (cortical or near-field response) of each hemisphere in response to contralateral median nerve shock-pulse stimulation. The lower trace represents the subject’s left and right hemisphere (cortical response) visual evoked potential following left eye strobe-light stimulation. In this and all subsequent illustrations, positive polarity is down. Note also the different sensitivity (ordinate) and the variations in latency (abscissa) with which data from each modality have been recorded and displayed.

have most often been used for clinical evoked potential studies (Fig. 1). Other sensory systems that have been used in man to evoke neuroelectric potentials are the olfactory, nociceptive, proprioceptive, and gustatory systems. Motor evoked potentials can also be recorded from the scalp, and reflect electrical activity of cortical motor neurons prior to the initiation of a voluntary muscle movement.

Signal Averaging

It is not feasible to record evoked potentials (EP’s) from scalp electrodes without signal averaging, because the amplitude of EP’s is one to three orders of magnitude less than the amplitude of EEG. Computers, now available at relatively low cost, can be used to extract the low-amplitude EP signal from the larger amplitude background electrical “noise” composed mainly of the EEG but also non-neural electrical activity. This equipment can also store the data on magnetic tape or disc, display it on an oscilloscope for photographic records, or plot the EP on graph paper. An example of computerized signal averaging is shown in Fig. 2 where the noise, spontaneous EEG, is progressively replaced by the completed EP after 512 time-locked EEG epochs have been averaged. Many studies describe in detail EP stimulation and recording techniques.

Clinical Significance of Evoked Potential Wave Components

Evoked potential wave components or peaks can be recorded from the scalp as early as a few milliseconds to several seconds following peripheral nerve stimulation. Electrical activity generated by structures in the spinal cord, brain stem, and cortex can be studied in these time periods. The latency from peripheral nerve stimulation to the generation of an EP wave component depends upon such factors as the patient’s body size, the position on the body where the stimulus is applied (Fig. 3), the conduction velocity of the axons in the respective neural pathways, the number of synapses in the system, the location of the neural generators of the EP component (brain stem, cortex), and the presence of
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Fig. 2. An example of computerized signal averaging compared to electroencephalographic (EEG) activity (top trace). The somatosensory evoked potential is displayed after 1, 8, 128, and 512 epochs of time-locked brain electrical activity have been averaged in response to right median nerve shock stimulation. The bottom trace represents electrical baseline, that is, 256 segments of “spontaneous” EEG activity averaged without the application of stimuli. Note the difference in amplitude (ordinate) and latency (abscissa) between EEG (top line) and the averaged evoked potentials.

CNS pathology. In scalp recordings, EP's arising from spinal cord or brain-stem structures occur within the first 10 to 15 msec after stimulation, whereas the EP wave components that follow those early electrical events are generated by more rostral structures in the thalamus and cortex.

Jewett and Williston introduced a technique for noninvasive scalp recording of brain-stem, early latency EP's of the human auditory system. Prior to this time, only EP's generated in the cortex were studied in man. These authors demonstrated that EP's recorded in the first 6 to 7 msec poststimulation are generated by elements of the auditory system located in the brain stem: they are called auditory brain-stem evoked potentials (ABEP's). Jewett and Williston distinguished ABEP's (far-field potentials, see below) from the auditory cortical evoked potentials generated in more rostral elements of the auditory system such as the cerebral cortex located nearer (near-field potentials, see below) to the recording scalp electrode.

The first five wave peaks of the ABEP's are thought to arise from the eighth nerve, cochlear nucleus, superior olivary complex, nucleus of the lateral lemniscus, and the inferior colliculus, respectively. Cracco, et al., demonstrated that spinal cord and somatosensory brain-stem evoked potentials (SBEP's) could be noninvasively recorded in man. Human spinal cord EP's are thought to arise in the dorsal columns following upper or lower extremity peripheral nerve depolarization.

The spinal cord potential will have a variable peak latency, depending on the location of the recording electrode with respect to the spinal cord and the location of stimulation (Fig. 5).

In man, there are three or four SBEP wave peaks that can be recorded by scalp electrodes within the first 15 msec poststimulation (Fig. 4). The generators of the first three or four peaks are not known with certainty. They may arise from elements of peripheral nerve (Erb's point potential), spinal cord dorsal columns, nuclei of the dorsal columns and/or medullary...
Erb's Point Triphasic Action Potential

Erb's - C7

0.62 μV

1 msec

Somatosensory Brainstem Evoked Potential

C7 - A1

0.31 μV

1 msec

Fig. 4. Human brain stem-generated evoked potentials (EP's) have been recorded in response to somatosensory and auditory stimulation. These short-latency EP components have small amplitudes in comparison to cortically generated evoked potentials (SEP, AEP). Many authors label only the positive wave peaks because electrical activity generated in the brain stem may be thought of as traveling toward scalp electrodes (the killed-end effect, see text and Fig. 6). The negative component (N1, lower left) is thought to represent the first cortically generated SEP wave.

Fig. 5. Bipolar recordings of the spinal potential evoked by left peroneal nerve stimulation. Interelectrode distance is 4.5 cm. Electrode 11 is placed over L-2 and Electrode 1 over C-3. For each trace, 8192 samples were averaged, and three separate averages are superimposed. The potential progressively increases in latency at more rostral recording locations. In the lead in which the caudal electrode is placed over T-9 (fourth trace from bottom), a complex potential with three negative components is recorded. (Reproduced with permission from Cracco RQ: Spinal evoked response. Peripheral nerve stimulation in man. Electroencephalogr Clin Neurophysiol 35:379–386, 1973.)

leminiscal pathway, and possibly from cerebellar and thalamic structures.2,5,26,61,69,73,124

While both brain-stem and cortical evoked potentials have been obtained in the auditory (AEP) and somatosensory (SEP) systems, only cortical EP's have been described for the visual system (VEP).4,18,19,72,102,121 This is probably a result of the masking effect that electroretinogram (ERG) potentials have on the early latency (0 to 40 msec) period of the VEP.17,27

Electrogenesis of Evoked Potentials

Two kinds of neuroelectric potentials may contribute to the genesis of the scalp-recorded evoked potential: 1) action potentials, and/or 2) graded postsynaptic potentials. Both of these depend on ionic current flow across neuronal membranes.

The action potential is an all-or-nothing transmembrane potential caused by neuronal depolarization. It can travel centrifugally or centripetally with respect to the brain. A recording electrode can detect the electrical activity caused by the action potential so long as it is in contact with the potential via a conductive medium, such as extracellular fluid or skin. As a propagated action potential approaches the recording electrode, an initially positive potential will be seen (Fig. 6B). When the depolarization is directly under the electrode, a negative potential is recorded (Fig. 6C). Finally, another positive component of the triphasic action potential will be recorded when the depolarization recedes from the electrode (Fig. 6D). An electrode positioned such that the action potential is always advancing toward it will record only a positive potential (killed-end effect, Fig. 6).79,124 This is why brain-stem EP wave peaks are often labeled only with positive polarity when recorded from the scalp.

Graded postsynaptic potentials (PSP's), on the other hand, are not all-or-nothing depolarizations of the neuron.29 They are subthreshold excitatory (EPSP's) or inhibitory (IPSP's) postsynaptic potentials that either bring the neuron closer to firing threshold, EPSP, or hyperpolarize the neuronal membrane and impede firing threshold from being attained, IPSP.
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TRIPHASIC ACTION POTENTIAL

A: + 1 + +
B: - + +
C: + + +
D: + + +

KILLED END EFFECT

1msec

Fig. 6. Simplified scheme represents extracellular recording of an action potential. A: With the neuron at rest, the extracellular electrode records no activity. B: Advancing depolarization generates low-amplitude positive component of triphasic action potential. C: Depolarization directly under the recording electrode generates a large negative potential. D: Receding depolarization produces a low-amplitude positive component of triphasic action potential. A killed-end effect can be seen if depolarization always approaches the recording electrode: the potential will be monophasic with a positive polarity.

The graded polarizations of the neuronal membrane may occur on the dendrites (Fig. 7), soma, or, perhaps, axonal hillock. Since the surface area of the dendritic tree is much greater than that of the soma or axon, most of the PSP's contributing to EP's are probably dendritic or dendrosomatic.

Volume Conduction, Near-Field and Far-Field Potentials

Evoked potentials recorded from the scalp are probably generated both by propagated action potentials in the axons of brain stem and/or hemispheric nerve tracts and by postsynaptic potentials of subcortical nuclei and cortical neurons. It is possible to record electrical potentials generated in subcortical structures of the brain stem from scalp electrodes because of the volume conduction properties of the intracranial contents.

Volume conduction theory describes the relationship between an electrical potential recorded directly from an active neuron and the same electrical potential recorded by electrodes placed some distance away but still in contact with the neuron through a conductive medium. Potentials recorded at a distance from their source through a volume conductor (far-field) behave differently than potentials propagated from a source close to the recording electrode (near-field) along a discrete length of nerve (propagated conduction). For example, in the case of an electrical potential that is volume-conducted: 1) it is difficult to locate the source of the active tissue because the current spreads diffusely throughout the conductive medium, namely, brain, cerebrospinal fluid, membranes; 2) as the distance between the recording electrode and current source is increased, so the recorded potential becomes smaller and slower (Fig. 8); and 3) the relationship between changes in the transmembrane potential and the resulting current flow in a volume conductor is very complex.

The shortest latency electrical potentials recorded following either somesthetic or auditory stimulation (SBEP and ABEP) are of small amplitude, and probably generated in peripheral nerve and brain-stem pathways. These are volume-conducted, detectable by scalp electrodes, and called “far-field potentials.” The far-field or brain-stem potentials occur within the first 15 msec following somesthetic stimulation at the wrist and 10 msec after auditory stimulation. It would appear likely that these potentials reflect temporally and spatially compact action potentials in peripheral nerves and lemniscal tracts. A contribution from post-synaptic potential is...
variations, depending on the electrode's location on the scalp. A recording electrode is moved from the source. Further movement of the electrode from the source of current will produce smaller amplitude changes. Thus, scalp-recorded spinal cord and/or brain-stem evoked potentials (EP's) will have a small, relatively constant amplitude while EP's resulting from cortical neuronal postsynaptic potentials have greater amplitude and will undergo more dramatic polarity variations, depending on the electrode's location on the scalp.

When cortical neurons in the visual, somesthetic, and auditory system are activated by sensory stimuli arriving at the cortex, EP waveforms are generated by postsynaptic potentials alone. These cortical EP's or near-field potentials may be divided into primary and secondary responses depending on their latencies. Primary cortical evoked responses result from the earliest electrical activity (PSP's) generated by cortical neurons. The location of the neurons that contribute to this response varies with the sensory system. It is thought that the primary cortical somesthetic response is generated in postcentral sulcus parietal neurons and has a latency of about 20 msec following median nerve stimulation at the wrist. The generator cells of the primary auditory cortical evoked potential may reside in Heschl's gyrus (this is a controversial issue) and have a latency of over 10 msec from time of stimulation. Visual primary cortical evoked potentials are probably masked by the large-amplitude electroretinogram (the ERG can easily be recorded by occipital electrodes) and have not been identified with certainty.

Primary cortical potentials have a relatively stable configuration compared to secondary cortical responses. The latter are of longer latency than the former and have variable waveforms. If primary cortical responses may be thought of as the response of primary sensory receiving neurons to stimuli, then secondary cortical potentials can be thought to arise in association cortex. Possible mechanisms for the generation of these secondary potentials include: 1) continued vertical processing of sensory information in the primary sensory receiving area without lateral spread to association cortex; 2) corticothalamic cortical reverberating circuits that periodically stimulate cortical neurons; and 3) diffuse cortical projection of extralemniscal slower electrical events possibly mediated by the reticular activating system or nonspecific thalamic nuclei.

**Interpretation of Evoked Potential Waveforms**

In a broad sense, there are two methods of interpreting EP's, based either on 1) their putative anatomical generators, or 2) the influence of psychological, cognitive, etc., brain function on cortical EP wave peaks. Whichever system is employed, it is vital to have precise, standardized stimulating and recording techniques so that data are accurately and reproducibly obtained. Furthermore, each EP laboratory must establish its own normative data bank to compare EP data from normal subjects with data recorded from patients with neurological disease. Such topics are beyond the intended scope of this article, but many excellent references are available.

**Anatomical Data Interpretation**

Interpretations based on anatomical methodology view EP waveform alterations caused by disease processes as the result of metabolic insults and/or anatomical lesions of specific cortical and subcortical structures in a neural system. For example, a brain-stem infarct or tumor that anatomically or functionally interrupts the auditory or somesthetic pathway may abolish all EP wave peaks that arise in tracts or nuclei distal to the lesion. In contrast, EP wave peaks may be unchanged or altered but not abolished if they have generators proximal to the lesion in neural structures that are intact.

The anatomical system in various forms is used most frequently for interpreting EP data in surgical and medical neurological practice. In this system, EP waveforms are analyzed by measuring in milliseconds the latency from time of stimulation to wave peak of interest and by measuring in microvolts the amplitude of the peak to following trough (Fig. 9). A wave peak may be identified by indicating its polarity (negative (N) or positive (P)), followed by its latency in milliseconds. To indicate the modality, either visual, auditory, or somatosensory, the prefix V, A, or S may be added. Thus, a positive peak in the somatosensory modality occurring at 15 msec from time of stimulation would be designated SP15. Other methods of labeling wave peaks are commonly used, but this one is rather simple and allows for frequent revision as new wave peaks are identified.

To be clinically effective, EP data analysis based on anatomical methodology fundamentally needs a well
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documented correlation between each EP wave peak, identified by amplitude and latency criteria, and its neural generator. Although significant progress has been made in the last 10 years to clarify the relationship of scalp-recorded EP's and their CNS sources, much is still unknown.\[^{51,124,126}\] Even less certain is the effect that metabolic and anatomic insults may have on EP wave peaks through compromise of neural substrata.\[^{170}\] Assuming that a wave peak has a single generator, then there are at least three ways for the EP peak to be altered as a result of brain compromise: 1) the generator itself is directly affected by the pathological process; 2) the neural pathway proximal to the generator passes through compromised brain; or 3) another structure distal to the generator that has a modulatory effect on it is destroyed.\[^{104}\]

Localization of dysfunction in brain regions (for example, differentiating brain-stem from hemispheric dysfunction) might best be accomplished by utilizing the wider scope afforded by multimodality evoked potentials (visual, auditory, and somatosensory) as opposed to one modality alone.\[^{50-57}\] Somatosensory and auditory sensory stimuli that generate both brain-stem and cortical EP's traverse regions of the brain stem, such as the medulla, pons, and midbrain, located caudal to the lateral geniculate bodies, the most caudal structures traversed by the sensory input that generates scalp-recordable VEP's (Figs. 1 and 10). Thus, abnormal or absent somatosensory and auditory brain-stem and cortical EP's recorded from comatose patients with normal VEP's could implicate dysfunctional brain stem more than dysfunctional cerebral hemispheres (Fig. 11).\[^{55}\] On the other hand, electrophysiological cerebral hemispheric dysfunction might exist if the data include normal auditory and somatosensory brain-stem potentials and abnormal visual, auditory, and somatosensory cortical potentials (Fig. 12).

![Fig. 9. This schematic drawing of somatosensory evoked potential (SEP) illustrates a method of analyzing and labeling waveforms. All waves, regardless of modality, are labeled as either positive or negative (P or N), followed by the latency from time of stimulation to wave peak in milliseconds. The SEP component amplitude may be calculated by measuring each wave from peak to following trough in microvolts.](image)

**Evoked Potential Data Interpretation Based on Cortical Function**

Evoked potential wave peaks of interest for investigating psychological and cognitive processes occur at longer latencies than those most frequently analyzed in attempts to localize areas of brain dysfunction or damage. The former occur at latencies beyond 100 msec and may well represent higher-level cerebral function. These longer latency wave peaks are often more difficult to analyze, as the subject's or patient's level of awareness, drug usage, and psychological state may significantly vary the evoked response from moment to moment.\[^{51}\]

A biphasic or triphasic EP can be recorded in the 100- to 300-msec latency range having maximal am-
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**BRAINSTEM LESION**

**SOMATOSENSORY EVOKED POTENTIAL**
MEDIAN NERVE STIMULATION

A.  L. PARIETAL LOBE  R. PARIETAL LOBE

1.25 µV
30 msec

B.  Cz-A1  Cz-A2

1.25 µV
60 msec

C.  L. OCCIPITAL LOBE  R. OCCIPITAL LOBE

2.5 µV
50 msec

D.  Tm-A2

EIGHTH NERVE ACTION POTENTIAL

AUDITORY EVOKED POTENTIAL

AUDITORY FAR FIELD

0.3 µV
6 msec

**FIG. 11.** Severely abnormal somatosensory and auditory cortical evoked potentials, with only slightly abnormal visual evoked potentials, in a patient with severely abnormal auditory brainstem evoked potentials indicate relatively greater brain-stem dysfunction than cortical dysfunction.

amplitude at the vertex in all modalities.\(^{34-36,51}\) Potentials in this time period may represent slow responses arising in association cortex as a late result of stimulation of primary cortex. However, another interpretation, especially following auditory stimulation, would place the generators of these potentials in subcortical structures or in diffuse areas of cortex stimulated by nonspecific ascending neural pathways. The so-called "vertex potential" presumably represents modality-nonspecific association cortex and is a useful tool in the study of mental illness. The vertex potential may have a different anatomical substrate than other longer-latency responses occurring between 100 to 300 msec generated by modality-specific primary and secondary cortex.\(^{78,111}\)

**Clinical Application of Evoked Potentials**

Clinical EP results are often reported with respect to the effect of disease entities on a single EP modality, such as alteration of the visual evoked response in patients with multiple sclerosis.\(^{8,12,59}\) We take an alternative approach where possible and discuss the effects of CNS disease on EP's in general, namely, visual, auditory, and somatosensory evoked potentials. Multiple sclerosis, for example, produces detectable changes in visual as well as auditory and somesthetic EP's because of the nature of the underlying functional abnormality.\(^{7,107,109,115}\) An eclectic approach, we believe, is instructive because it emphasizes disease pathophysiology and the relatively similar manner in which all EP modalities behave following CNS compromise. Any insult sufficient to alter neuronal metabolism or perturb membrane function may alter evoked neuroelectric activity regardless of the etiology of the insult or the modality of the EP.\(^{56}\)

Interpretation of clinical EP data in the sections that follow is based mostly on an anatomical perspective, as this approach has frequently been taken in clinical studies. Finally, it cannot be over-emphasized that meaningful clinical utilization of EP data is contingent on meticulous stimulating and recording techniques. Neurogenic, myogenic, and environmental contamination must be recognized and eliminated so that data is artifact-free.

**Demyelinating Diseases**

Demyelinated neurons respond to depolarization with a complete block of conduction or a slowing of conduction, and an increase in their refractory period.\(^{59}\) As a result of the prolonged refractory period, faster trains of impulses may fail to conduct. Body
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**AUDITORY BRAINSTEM POTENTIALS**

- **Left Hemisphere**
  - 0.15 μV
  - 4.0 msec
- **Right Hemisphere**
  - 2.50 μV
  - 20.0 msec

**SOMATOSENSORY**

- **Left Hemisphere**
  - 10.0 μV
  - 40.0 msec
- **Right Hemisphere**
  - 2.50 μV
  - 20.0 msec

**VISUAL**

- **Left Hemisphere**
  - 10.0 μV
  - 40.0 msec
- **Right Hemisphere**
  - 2.50 μV
  - 20.0 msec

**FIG. 12.** Dysfunction of the cortex is greater than that of the brain stem in this patient. Both the somatosensory and visual cortical evoked potentials are severely abnormal while the auditory brain-stem evoked potentials are only slightly abnormal (see text for explanation).

Temperature is also an important variable. As the degree of demyelination increases, complete conduction blockade occurs at lower body temperatures. Diseases such as multiple sclerosis, central pontine myelinolysis, and progressive multifocal leukoencephalopathy have been studied with EP analysis. Because the diagnosis of multiple sclerosis may depend on identifying CNS dysfunction in more than one area, and because of the waxing and waning of the disease process as well as its disseminated CNS localization, clinical utilization of all EP modalities has become widespread.

Assessments of peripheral and central conduction in the somatosensory system to both median nerve and peroneal nerve stimulation have been fruitful. Dorfman, et al., demonstrated that, in patients with multiple sclerosis in whom sensory symptoms or signs were present, it was possible to crudely localize the level of sensory lesion to spinal or supraspinal pathways. If the cortical SEP in response to peroneal nerve stimulation at the ankle was normal, they were always able to record a normal SEP in response to median nerve stimulation. Eisen and Odusote reported a similar observation following stimulation of the tibial nerves. They noted that lower extremity stimulation allowed for greater sampling of the CNS than did upper extremity stimulation, and produced a higher yield of abnormal SEP data in multiple sclerosis patients. These authors also evaluated somatosensory central conduction (see below, section on head injury) in patients with multiple sclerosis by measuring the latency between the SEP wave peak generated in the medulla and the first wave peak generated in the cortex. Their reported normal mean value for central conduction thus derived was 5.45 ± 0.7 msec (a prolongation greater than 7.5 msec was considered abnormal).

In 1972, Halliday, et al., noted an increase in latency of the P_{100} component of the reversible checkerboard-pattern visual evoked potential (PVEP) in patients with multiple sclerosis. They reported that the P_{100} component produced by PVEP is more stable than components generated by the flash of a strobe light. A latency increase in the P_{100} was considered diagnostic of optic nerve dysfunction, and was found to be present in patients with suspected multiple sclerosis who had normal optic discs, fields, and fundi. The PVEP's rather than the flash-generated VEP's are more frequently altered because demyelinating lesions occur more frequently in fibers subserving central vision, the fibers that are probably stimulated by PVEP. Flash VEP's may be mediated by the entire retina. Many authors have subsequently confirmed the sensitivity of PVEP in detecting optic nerve demyelination. Trojaborg and Petersen also studied multiple sclerosis patients with PVEP, but were successful in detecting abnormalities in only 70% of patients with established or suspected multiple sclerosis.
sclerosis, whereas Halliday, et al.\textsuperscript{50} reported PVEP abnormalities in greater than 90% of these patients. When Trojanbarg and Petersen\textsuperscript{115} added SEP abnormalities and PVEP abnormalities, their EP diagnostic yield in multiple sclerosis patients exceeded 90%. Asselman, et al.,\textsuperscript{6} in an excellent review of PVEP, reported P\textsubscript{100} delays in 67% of patients with multiple sclerosis. Moreover, they caution against an over-optimistic view of the specificity of PVEP in detecting optic neuritis secondary to demyelinating disease because pattern luminescence, pattern reversal speed, and the clinical definition used to identify multiple sclerosis patients are all important variables that need to be carefully controlled.

Demyelinating lesions of the brain stem were detected by abnormalities of the ABEP in 48% of 135 patients with suspected multiple sclerosis tested by Stockard, et al.\textsuperscript{110} Multiple sclerosis patients had interpeak latency prolongations of selected components of the ABEP. The authors suggested that the ABEP is more sensitive to white matter disease than gray matter alterations. For example, in patients with progressive supranuclear palsy, the earliest peaks, P\textsubscript{1} and P\textsubscript{2}, generated by the eighth nerve and cochlear nucleus, either absent or abnormal, and a loss of subsequent longer-latency ABEP waves. Furthermore, they reported that brain-stem gliomas were associated with a greater than 90% prevalence of ABEP abnormalities as they often infiltrate widely prior to clinical decompensation. These authors and others have correctly localized intracranial tumors (such as germinoma of the pineal area, metastatic carcinoma, brain-stem meningioma, acoustic neuroma) to the peripheral, pontomedullary, pontine, midbrain, and thalamic regions by studying changes in ABEP wave peaks.\textsuperscript{31,96,104-107,109,110,113} The ABEP recording can also be serially repeated to monitor tumor growth, suggesting extension of tumor caudally, or to follow the regression of a pinealoma after radiation therapy.\textsuperscript{107}

Of all posterior fossa tumors studied with AEP techniques, acoustic nerve tumors have generated the greatest interest. Shimizu\textsuperscript{99} noted that, as the number of eighth nerve tumor cases under study increased, more cases with atypical audiological findings were discovered. The many psychoacoustic tests (such as alternate binaural loudness balance (ABLB), SISI, and Bekesy audiometry tests), although highly useful, are not infallible.\textsuperscript{99} There has been constant search for more reliable methods of diagnosing acoustic tumors and cerebellopontine angle tumors at an early stage.\textsuperscript{113} There is an inverse relationship between the operability of acoustic tumors and their detectability.\textsuperscript{98} Larger tumors are easier to diagnose but more difficult to remove safely.\textsuperscript{98}

Many authors have studied ABEP changes in patients with cerebellopontine angle tumors.\textsuperscript{98,106,109,113} In these cases, the first one or two ABEP peaks, generated by the eighth nerve and cochlear nucleus following unilateral stimulation of an affected side, are either the only ABEP wave peaks present
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or are delayed in latency and have amplitude reductions.105-107,109 Selters and Brackmann86 compared the latency of the ABEP peak P5, thought to arise in the pontomesencephalic area, on the affected side to that of the normal side. Normal interaural P3 latency differences are less than 0.2 msec but were 0.4 msec or greater for 36 patients with documented tumors. Daly, et al.,31 evaluated four patients with acoustic neuroma using varying interstimulus intervals. They found that abnormalities in ABEP increased on the affected side with shorter interstimulus intervals. When cerebellopontine angle tumors compress the brain stem but spare the eighth nerve, ABEP abnormalities are found in wave peaks generated in the pons or more rostral structures of the auditory pathway.

Somatosensory evoked potential (SEP) components, both cortical and brain stem, have often been used to diagnose and manage intracranial tumors. Interestingly, during acoustic tumor surgery, the SBEP can be used to intraoperatively monitor brain-stem function, when the ABEP cannot be recorded for this purpose because of eighth nerve compromise. Tumors of the thalamus (glioma) spare the somatosensory peak P15 but abolish all later activity.84 However, tumors of the primary sensory receiving area of the parietal lobe (meningioma) can also reproduce this SEP pattern.84 The P15 peak is generated in the brain stem caudal to the thalamus.2,5,14,69,75,124 An SEP wave peak generated by the thalamus itself has not been consistently demonstrated in man. Yamada, et al.,126 showed that SEP's generated by bilateral simultaneous median nerve stimulation were sensitive indicators of unilateral dysfunction of the parietal and frontal lobes caused by tumors affecting the cortex.

As early as 1964, Vaughan and Katzman119 evaluated visual pathway dysfunction with strobe light-generated VEP's and electroretinography (ERG). They noted normal ERG but absent VEP in a case of unilateral optic glioma in a 22-month-old baby with proptosis. In another patient with bitemporal hemianopsia secondary to a pituitary tumor, VEP's distinguished the side that had extensive optic nerve involvement compared to the side with greater chiasmal involvement. These authors also reported an occipital lesion secondary to metastatic carcinoma that was detectable by the suppression of early cortical waves. Using reversing checkerboard, black-white, retinal stimuli, Halliday, et al.,94 diagnosed multiple sclerosis in 60% to 90% of patients and optic neuritis in over 90% of patients whose disease was clinically confirmed. They noted, however, that the delayed-latency PVEP recorded from multiple sclerosis patients was not specific, and could also be obtained in patients with anterior visual pathway compression. Nineteen patients were studied, four had tumors of the orbit (two cavernous hemangioma, one neurilemoma, one meningioma), two sphenoid wing meningiomas, three suprasellar meningiomas, two craniopharyngiomas, and eight pituitary tumors. The characteristics of the PVEP changes encountered in patients with anterior visual pathway compression were different from those in patients with demyelinating diseases. Although an abnormal PVEP was found in 18 of 19 cases, the incidence of delayed response was small (four of 19) in cases of anterior visual pathway tumor compression compared to multiple sclerosis patients, as was the incidence of waveform alterations. No single change in pattern response appeared pathognomonic in patients with tumor compression. Holder86 supported the finding that PVEP abnormalities were present in most patients with anterior visual pathway compression secondary to tumor; he reported PVEP changes in 10 of 10 patients studied (eight with pituitary tumors, one craniopharyngioma, and one aneurysm). Latency delays and diminished amplitudes were found in response to monocular stimulation.

Continuous intraoperative monitoring of visual function with VEP's has been accomplished during parasellar surgery. Feinsod, et al.,44 reported that, during the surgical removal of a pituitary adenoma, prolongation of VEP latency and deterioration of wave patterns could be noted when the optic nerves were manipulated. Furthermore, recovery of the VEP waveform recorded following stimulation of the impaired eye began as early as 10 minutes after surgical decompression of the optic nerve. The effect of manipulation of the optic nerves and chiasm and occlusion of perichiasmal vessels was evaluated continuously during surgery by Wilson, et al.123 They reported that changes of the baseline VEP caused by manipulation were reversible and were probably secondary to transient ischemia.

Head Injury

Severe head injury causes diffuse brain damage and dysfunction as a direct result of the energy dissipated in brain tissue and, secondarily, because of lesions such as hematomas, elevated intracranial pressure (ICP), brain herniation, and ischemic insults. Because of the several mechanisms of injury and the disseminated location of lesions, it is difficult to completely evaluate brain dysfunction or the efficacy of treatment in head-injured patients.55,57 Furthermore, inability to communicate with comatose patients limits information obtainable from the neurological examination. These problems have stimulated considerable interest in EP's as another means of evaluating the location and extent of areas of brain dysfunction following head injury.32,43,55-57,64,65,76,86,93,94,97,118,119

Larson, et al.,76 evaluated 15 head-injured patients with automated on-line SEP's, and concluded that SEP's were sensitive to hypoxia, ischemia, compressive phenomena, and other adverse changes in the neuronal environment. Specifically, they reported that when cerebral blood flow was initially reduced, SEP amplitude decreased but latency and waveform re-
mained unchanged. Compressive lesions, such as subdural hematoma, caused latency increases and a trend toward loss of waveform complexity. Changes in level of responsiveness could not be correlated with SEP data. A similar simplification of the complex SEP waveform was reported by de la Torre, et al.,32 in a study of 17 comatose head-injured patients. They reported that patients with eight identifiable SEP wave peaks in the first 300 msec following bilateral median or peroneal nerve stimulation had good outcomes. When only five peaks remained in the first 500 msec following head injury, the patients had poor outcomes. If only the first two primary SEP peaks remained, no recovery could be expected. Secondary cortical SEP waves appeared more critical for return of consciousness. These authors also stated that autopsy and computerized tomography (CT) findings did not closely correlate with SEP, as the former represent anatomical data and the latter functional data.

By analyzing the time delay occurring between an EP generated in a brain-stem structure and the first cortical potential recordable, a measure of central brain conduction time can be obtained.34,63 Central conduction as calculated in the somatosensory system can be derived by subtracting the latency of the potential generated in the medulla, \( P_3 \) (approximately 14 msec after stimulation), from that of the potential generated by somatosensory cortex, \( N_1 \) (approximately 20 msec after stimulation) (Fig. 4).64 This latency is independent of body size and peripheral nerve conduction velocity, and may also be independent of body temperature and serum barbiturate level. Changes in central conduction time may result from cortical dysfunction, abnormal synaptic delay in the thalamus, cortex, or both, and slowed axonal conduction. Hume, et al.,65 studied SEP central conduction time in comatose patients, many of whom had head injuries. They reported that central conduction time at both 10 and 35 days after injury significantly correlated with the patients’ outcome. All patients who made a good recovery had normal conduction times at or before the end of the 35-day period. In 11 of 13 patients who did not make a good recovery, either the conduction time remained abnormal or the cortical SEP's could not be recorded. The authors speculated that failure of transmission in the somatosensory system is most likely secondary to shear strains at impact or ischemia.

Coma caused by drug overdose (such as barbiturates, diazepam, glutethimide, amitriptyline) or metabolic conditions (such as diabetic ketoacidosis, anemia, hepatic failure, meningitis) can be distinguished from coma caused by brain-stem damage by means of ABEP's.104,105 Starr and Achor105 reported that, in some comatose patients with toxic or metabolic coma, the ABEP's were normal when spontaneous respiration, cold caloric responses, and oculocephalic reflexes were absent or depressed. If the cortex is not irremediably damaged, comatose patients with normal ABEP's may make excellent recoveries.

In a study of the relationship between brain-stem reflexes, levels of coma, and ABEP's, Uziel and Benezech118 reported their results in 20 comatose patients, 75% of whom had head injury. They noted, as have others,57,94,98,106,110 that the first five wave peaks of the auditory evoked potential are thought to arise from a sequence of caudal-rostral oriented generators in the auditory neural pathway. Three ABEP wave peaks are particularly robust: Wave I, pontomedullary; Wave III, pontine; and Wave V, rostral pontine-collicular region. In flaccid patients, generally only Wave I was present, while patients with bilaterally reactive pupillary dilatation had abnormalities of Wave I, II, or III. Decerebration was present in 11 patients. Eight of these patients had no abnormalities of their ABEP. The remaining three patients had only mild EP abnormalities. Those patients in an apallic state also had no ABEP changes, confirming the rostral location of lesions producing this clinical picture. Seales, et al.,97 evaluated brain-stem function in 17 comatose head-injured patients with ABEP recording. They reported that abnormalities of these EP's were reversible when recorded in the first 2 to 3 days following head injury. Thus, the prognostic value of the ABEP increased after the 3rd day following injury. They also indicated, as have others,55,57,76 that EP's can be used to monitor brain-stem function in the intensive care unit and to assess the effect of treatment on brain-stem function.

Vaughan and Katzman119 were the first to suggest that simultaneous recording of the electroretinogram and VEP generated by each eye separately was a useful clinical method to localize optic system dysfunction following head injury. If the electroretinogram17 was normal and no VEP was obtained, optic nerve trauma was considered likely.119 In trauma patients without detectable VEP's or electroretinograms, local eye trauma was probable.44,110 Bergström and Nyström5 studied VEP's in three groups: normal individuals, patients with VEP abnormalities without loss of consciousness, and patients with VEP abnormalities with loss of consciousness. They reported that organic visual system defects can produce VEP changes regardless of the patient's level of consciousness.9

Multimodal sensory EP techniques have also been applied to the evaluation of brain function in head-injured patients.55-57,83,94 Rappaport, et al.,94 studied five cases of head injury with VEP's and AEP's to help in the development or rehabilitation plans. Greenberg, et al.,56-57 evaluated comatose patients with severe head injury using multimodality EP monitoring (VEP, SEP, AEP, ABEP, and SBEP), and were able to recognize four basic patterns of abnormality in each EP modality. These patterns were graded I to IV, based on a progressive reduction in waveform complexity. Correlation of the graded evoked poten-
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...tals and patient outcomes was strong.55,57 Mildly abnormal EP's, Grades I and II, were predictive of good to moderate outcomes in 81% of patients. When patients dying of secondary systemic insults were removed from analysis, the prognostic accuracy of EP's obtained in the first 24 to 48 hours following injury improved to over 90%.57

These authors also compared the predictive accuracy of multimodality evoked potentials (MEP's) to that of single clinical neurological signs such as motor posturing, pupillary light reflexes, oculocephalic/oculovestibular responses, and combinations of clinical signs such as the best five clinical signs or the Glasgow Coma Scale (GCS).86 Furthermore, CT findings and ICP measurements were evaluated separately and in combination with the neurological and MEP data to assess their prognostic accuracy. They reported that MEP data were the most accurate and reliable single prognostic indicators, with 91% accuracy of prediction.86 These data were followed by age, ICP, pupillary response to light, extraocular motility, and motor posturing in decreasing order of prognostic accuracy. The combination of clinical signs, age, pupillary response, extraocular motility, and motor posturing correctly predicted outcome with 82% accuracy. The GCS alone accurately forecast outcome in 80% of cases. Addition of MEP results to clinical data improved accuracy to 89% and provided the most reliable predictions of any combination of data (64% of predictions made above the 90% confidence level). Whether analyzed alone or in combination with neurological, CT, or ICP data, MEP's appeared to have high prognostic value in severe human head trauma.86

**Disease of Spinal Cord and Brachial Plexus**

Evaluation of human spinal cord function with SEP's was one of the earliest clinical applications of the EP technique.47,48,61 By stimulating upper or lower extremity peripheral nerves and recording the resultant cortical SEP from the scalp, Giblin,47,48 and Halliday and Wakefield61 studied patients with such spinal cord diseases as syringomyelia, cervical spondylosis, thoracic disc protrusion, thoracic meningioma, trauma, basilar invagination, spinocerebellar degeneration, and vascular lesions of the cord. Regardless of the disease studied, patients with intact, functioning dorsal columns had normal SEP's, whereas patients with loss of vibratory and joint position sense always had compromised EP's. These authors concluded that the dorsal columns were necessary for the transmission of SEP's through the spinal cord.47,48,61 Namerow85 and Larson, et al.,77 demonstrated no SEP alterations in patients studied before and after spinocerebellar cordotomies. Thus, spinocerebellar tract function is not a necessary condition for recording cortical SEP's following shock-pulse peripheral nerve depolarization. When brief laser pulses sufficient to stimulate pain nerve endings without causing tissue damage are used as stimuli, an SEP can be obtained that is transmitted through the spinocerebellar tract.18 Because of the relative ease with which a peripheral nerve can be depolarized by shock pulse, this type of SEP stimulation rather than the laser has most often been applied in clinical settings.

Perof89,90 reported observations in patients with spinal cord injury in whom attempts were made to record SEP's from the scalp following peroneal, median, and ulnar nerve depolarization. No patient with a clinically complete cord lesion had an SEP following stimulation of the peroneal or sural nerves. In about 50% of patients with incomplete lesions, SEP's were present in scalp recordings. Median nerve stimulation was found to produce an SEP with lesions caudal to the C6-7 vertebral segment, but not with those rostral to this cord level. Incomplete lesions caused abnormal SEP's characterized by increased peak latencies and decreased peak amplitudes. Bricolo, et al.,11 monitored spinal cord function with scalp-recorded SEP's before, during, and after therapeutic cord hypothermia at 5°C in patients with clinically complete spinal cord transections. Seven of the 11 patients reported made a complete or partial clinical recovery; SEP's were obtainable in all seven patients. When an SEP could not be recorded, clinical recovery did not occur. Clinical recovery was associated in all cases with improvement of SEP's.

Spinal cord function has been directly evaluated by intraoperative cord stimulation and recording, as well as by nonoperative invasive needle techniques.39,40,41 Intrathecal measurements of maximum cord conduction velocity from the lumbosacral to the cervical cord enlargements have been obtained and range from 30 to 50 msec.42 Cracco, et al.,22 described a technique for noninvasive recording of spinal EP's. An array of recording electrodes was placed on the skin directly overlying the spinal cord in a rostrocaudal direction, and upper or lower extremity peripheral nerves were stimulated (Fig. 5). A triphasic spinal potential was recorded that appeared to originate in the dorsal funiculus.21-23,25,28 The conduction velocity of this potential was measured at 60 to 80 meters/sec, and slowed in more rostral segments of the cord. The initial positive component of the triphasic potential recorded from the spinal cord may represent the dorsal root fiber afferent volley. The negative component may have contributions from a number of structures, such as afferent cord terminals, interneurons and/or neurons in the dorsal horn, and postsynaptic potentials in the gray matter. The trailing positive component may reflect depolarization potentials of motor neurons in the anterior horn, or primary afferent depolarizations.28,41,42 It has been possible with this technique to identify more accurately the location of spinal cord compromise.24

Intraoperative measurement of spinal EP's has been utilized for a variety of problems in which careful monitoring of spinal cord function is desirable.40-42,90 The care of patients with disorders such as tumors of
the spine, unstable neck fractures, spinal cord trauma, and severe cervical arthritic changes may be improved after the induction of surgical anesthesia if cord function is monitored during positioning of the patient on the operating table. Patients undergoing operative correction of progressive scoliosis secondary to such diseases as myotonia dystrophica, Duchenne muscular dystrophy, and neurofibromatosis have also benefitted from intraoperative EP monitoring of spinal cord function.40

Matsukado, et al.,40 used EP's to study nine patients who had cervical spondylotic myelopathy and two patients who had disc protrusions. An epidural electrode was placed at the level of surgery and another was placed one to two segments rostral to that point. They reported that the spinal EP was an indicator in forecasting patients who would make a good recovery from the myelopathy as opposed to those who would not, by the degree of electrical abnormality found at surgery.

Prognosis for brachial plexus lesions proximal to the dorsal root ganglia is poor.60 Reconstructive surgery following transections of peripheral nerves distal to the ganglia may sometimes be effective.60 Jones and others6 have reported on the use of SBEP to supplement existing, relatively indirect methods of distinguishing between brachial plexus traction lesions distal and proximal to the dorsal root ganglia. If the Erb's point action potential (Fig. 4) to median nerve stimulation was present, the lesion was thought to be proximal to the ganglion. The SBEP wave peak thought to arise in the medulla was absent in these cases (Fig. 4). In patients who did not have an Erb's point potential, the lesion was found distal to the ganglion. Correct preoperative localization of the lesion was accomplished with SBEP in eight of 10 cases.60

Conclusions

Recent successful applications of EP’s to problems in the clinical neurosciences are in part the result of improved computer technology, equipment refinements, and more sophisticated methods of stimulating the CNS. However, the capacity to noninvasively record human brain stem-generated evoked potentials (techniques for this were first introduced in the early 1970's) provided perhaps the major impetus to the entire field of clinical EP recording. We have reviewed only some of the many applications of both brainstem and cortical recording techniques in the clinical neurosciences. There are many others.9,10,13,21,30,49,53,54,70,73,74,87,101,103,112,117,122,126

Whether evaluating CNS function by means of a single neural pathway or by a multimodal approach, EP’s can provide clinical neuroscientists with functional information that is both complementary and supplementary to that of the clinical neurological examination. Because of its proven and potential value, this electrophysiological technique deserves continued support and further study.

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*Address reprint requests to: Richard P. Greenberg, M.D., Ph.D., Division of Neurosurgery, Box 631, MCV Station, Richmond, Virginia 23298.*